AMENDMENTS TO THE CLAIMS

Claims 1-83 (cancelled)

84. (new) A method of producing a comminuted sterile suspension of particles, which comprises:

subjecting an initial sterile suspension of particles to a comminution procedure carried out in a sterilized particle size reduction apparatus, said particle size reduction apparatus comprising an interaction chamber for reducing the particle size of the suspension, and an intensifier for introducing the suspension into the interaction chamber at high pressure, and recovering a suspension of particles of reduced size;

characterized in that components of the particle size reduction apparatus are sterilizable and the method includes a sterilization step in which at least surfaces of the apparatus contacting the suspension are sterilized.

85. (new) A method according to Claim 84, wherein the sterile suspension comprises Budesonide or Fluticasone.

86. (new) A method according to Claim 84, wherein particle size is monitored until a final particle size in the suspension of mass median diameter 2-3 μm is obtained.

87. (new) A method according to Claim 84, further comprising the step of packaging the sterile suspension into sterile ampoules.

88. (new) A sterile suspension prepared according to Claim 84.

89. (new) A sterilizable particle size reduction apparatus for use in the method of Claim 84, comprising an interaction chamber for reducing the particle size of a suspension, and an intensifier for introducing the suspension into the interaction chamber at high pressure.

90. (new) Apparatus according to Claim 89, wherein the intensifier comprises an output and an input, and the interaction chamber comprises an input and an output, the output of the intensifier being connected to the input of the interaction chamber and the output of the interaction chamber being connected to the input of the intensifier, and wherein there is no conduit between the output of the intensifier and the input of the intensifier other than via the interaction chamber.

91. (new) Apparatus according to Claim 89, wherein valves in the conduits between the intensifier and the interaction chamber are sterilizable diaphragm needle valves.

92. (new) Apparatus according to Claim 89, wherein the intensifier comprises a bore and a reciprocating plunger and a seal between the plunger and the bore.

93. (new) Apparatus according to Claim 92, wherein the seal is an annular high-pressure seal, for a plunger reciprocating within a barrel, comprising lower and upper body portions, said upper portion being in the form of a cup and having sides surrounding a recess, the sides being outwardly deformable so that respective outer and inner edges of the sides of the cup make, in use, sealing contact with respectively the barrel and the plunger, the seal further comprising a brace to prevent the sides from collapsing into the recess under low pressure and wherein the brace comprises a resilient plastics material.

94. (new) Apparatus according to Claim 92, wherein the seal is an annular high-pressure seal, for a plunger reciprocating within a barrel, comprising lower and upper body portions, said upper portion being in the form of a cup and having sides surrounding a recess, the sides being outwardly deformable so that respective outer and inner edges of the sides of the cup make, in use, sealing contact with respectively the barrel and the plunger, the seal further comprising a brace to prevent the sides from collapsing into the recess under low pressure and wherein the seal is sterilizable.

95. (new) Apparatus according to Claim 93, wherein said brace presents a smooth surface free from cavities.

96. (new) Apparatus according to Claim 93, wherein said plastics material is disposed in said recess.

97. (new) Apparatus according to Claim 96, wherein said plastics material fills said recess so that the upper surface of said plastics material is level with or nearly level with the height of said cup sides.

98. (new) Apparatus according to Claim 93, further comprising a metal spring.

99. (new) Apparatus according to Claim 98, wherein the metal spring is enclosed within the resilient plastics material of the brace.

100. (new) Apparatus according to Claim 93, wherein said seal is operable at temperatures up to 75°C.

101. (new) Apparatus according to Claim 93, wherein said seal is operable at temperatures up to 90°C.

102. (new) Apparatus according to Claim 93, wherein said seal is operable at temperatures up to 122°C.

103. (new) Apparatus according to Claim 100, wherein said seal material is virgin PTFE or glass-strengthened PTFE.

104. (new) Apparatus according to Claim 93, wherein said brace is manufactured from a different material to that of the other seal components.

105. (new) Apparatus plunger seal according to Claim 104, wherein the resilient plastics material of the brace is more flexible than the material of the upper and lower body portions of the seal.

106. (new) Apparatus according to Claim 89, wherein the intensifier comprises a reciprocating plunger, and a bushing assembly, to guide the plunger, wherein the bushing assembly comprises a channel in or on the surface of the bushing assembly to allow steam or water to pass through the bushing assembly whilst the plunger is in place.

107. (new) Apparatus according to Claim 106, wherein the bushing assembly for use with a cylindrical plunger, comprises a bushing holder and a bushing, held in place by the

bushing holder, wherein the bushing assembly comprises one or more conduits to allow passage of sterilizing steam or water therethrough.

108. (new) Apparatus according to Claim 107 wherein the plunger reciprocates in a plunger barrel, and the bushing holder attaches to a neck of the barrel and the bushing is held in place by the bushing holder and which guides the plunger into and out of the barrel, wherein the bushing and/or the bushing holder comprises one or more conduits to allow passage of sterilizing steam or water through the bushing assembly.

109. (new) Apparatus according to Claim 107, wherein said bushing comprises one or more grooves located on its outer surface.

110. (new) Apparatus according to Claim 107, wherein said bushing comprises one or more grooves located on its inner surface.

111. (new) Apparatus according to Claim 109, wherein said one or more grooves are parallel to the longitudinal axis of the bushing.

112. (new) Apparatus according to Claim 109, wherein said one or more grooves are formed in a spiral around the longitudinal axis of the bushing.

113. (new) Apparatus according to Claims 107, wherein the bushing comprises one or more grooves and the bushing holder comprises one or more grooves or one or more conduits to allow passage of sterilizing steam or water therethrough.

114. (new) Apparatus according to Claim 113, wherein said one or more grooves of said bushing and bushing holder are in alignment.

115. (new) Apparatus according to Claim 114, wherein said bushing further comprises one or more projections that cooperate with one or more recesses in said bushing holder in order to align said one or more grooves of said bushing with those of the bushing holder.

116. (new) Apparatus according to Claim 114, wherein said bushing holder further comprises one or more projections that cooperate with one or more recesses in the bushing in order to align said one or more grooves of said bushing with those of the bushing holder.

117. (new) Apparatus according to Claim 89, wherein the intensifier comprises a plunger connected via a threaded cam nut to a connecting rod, at one end of which connecting rod is a screw thread to receive the cam nut, and wherein the dimensions of the screw thread and the thread of the cam nut are such that as the nut is screwed onto the connecting rod, and wherein respective mating surfaces of the cam nut and the connecting rod mate simultaneously.

118. (new) Apparatus according to Claim 89, comprising a heat exchanger to maintain the temperature of the suspension at from 7°C to 40°C in use.

119. (new) Apparatus according to Claim 89, comprising a pressure relief valve which is a rupture disc.

120. (new) Apparatus according to Claim 89, wherein non-return valves in conduits between the intensifier and the interaction chamber have metal-to-metal seats.

121. (new) Apparatus according to Claim 89, comprising a first heat exchanger to maintain temperature of the suspension in the interaction chamber and a second heat exchanger to maintain temperature of the suspension in the intensifier, wherein the first and second heat exchangers are independently controlled.

122. (new) Apparatus according to Claim 89, comprising a seal that prevents suspension from reaching the oil that drives the intensifier, for example in the event of failure of a plunger seal in the intensifier.

123. (new) A method of sterilizing a particle size reduction apparatus according to Claim 89, comprising charging the apparatus with steam, to achieve sterilization.

124. (new) A method according to Claim 123, comprising validating sterilization.

125. (new) A method according to Claim 123, comprising insulating valves and conduits downstream of the interaction chamber, so as to maintain steam temperature during sterilization.

126. (new) A method according to Claim 123, comprising:

connecting steam traps to the apparatus;

connecting temperature monitors to the apparatus;

introducing steam into the apparatus;

monitoring temperature at each of the temperature monitors;

noting the time at which temperature recorded by each of the temperature monitors has reached the sterilizing temperature;

continuing to introduce steam into the apparatus for a predetermined period.

127. (new) A method according to Claim 126, wherein the period is determined by:

introducing heat-resistant bacterial spores into the apparatus;

introducing steam into the apparatus and monitoring apparatus temperature until it has reached the sterilizing temperature;

continuing to introduce steam for a first known amount of time;

determining whether after that first known amount of time sterilization has been achieved; and

if sterilization has not been achieved, repeating the method for a second, longer known amount of time.

128. (new) A method according to Claim 127, wherein sterilization is deemed to have occurred when a six log reduction in heat-resistant bacterial spores has been achieved.

129. (new) A method according to Claim 126, wherein the sterilizing temperature is 121°C.

130. (new) A method according to Claim 123, comprising introducing steam into the intensifier and downstream of the interaction chambers.

131. (new) A method according to Claim 123, comprising pre-heating the interaction chambers.

132. (new) A method according to Claim 123, wherein all steam exiting the intensifier passes through the interaction chambers.

133. (new) A method of sterilizing a particle size reduction apparatus according to Claim 89, comprising charging the apparatus with pressurized superheated water so as to sterilize the apparatus.

134. (new) A method according to Claim 133, comprising operating the intensifier so as to control the temperature of the water during sterilization.

135. (new) A method according to Claim 134, comprising adjusting pressure within the apparatus so as to adjust temperature within the apparatus.

136. (new) A method according to Claim 133, comprising introducing the water into the intensifier and introducing steam into the isolation area of the intensifier, the steam being at the same temperature as or at a higher temperature than the water.

137. (new) A method according to Claim 136, wherein the steam is at least 0.5°C higher than the water.

138. (new) A method according to Claim 134, comprising:

introducing water at a temperature below 100°C into the apparatus; and

operating the apparatus so as to increase the temperature of the water to the sterilizing temperature.

139. (new) A method according to Claim 138, wherein the sterilizing temperature is 121°C.

140. (new) A method according to Claim 133, comprising flushing the apparatus with sterile air once the apparatus has been sterilized.

141. (new) A method according to Claim 133, wherein the pressurized, superheated water comprises a surfactant.